OIPE JC67
JUL 24 2000
PATENT & TRADEMARK OFFICE

#20
08/22/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	)	Group Art Unit 1641
	)	
Duft, et al.	)	Examiner S. Devi
	)	
Serial No. 08/870,762	)	
	)	
Filed: June 6, 1997	)	
	)	
For: **METHODS FOR TREATING OBESITY**	)	

APPEAL BRIEF

Real Party in Interest

The real party in interest is Amylin Pharmaceuticals, Inc.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1-6 as they appear in Appendix One stand finally rejected and are appealed.

RECEIVED
JUL 28 2000
TECH CENTER 3600

Status of Amendments

Claim 1 was amended subsequent to the final rejection that forms the basis for appeal. That amendment has been entered. See Advisory Action, Paper No. 18.

Summary of Invention

Amylin Pharmaceuticals, Inc., owner of the subject application, was formed in 1987 by Dr. Garth Cooper following his discovery of amylin at the University of Oxford in England. Amylin is a 37 amino acid, carboxy-terminally amidated peptide. Dr. Cooper's work also showed that amylin is a hormone involved in fuel metabolism. It is co-secreted with insulin in response to a meal.

In the years following the discovery of amylin and the founding of Amylin Pharmaceuticals, scientists at Amylin have been responsible for elucidating much of what is now known about the chemistry, biology, and physiology of the amylin molecule. Amylin Pharmaceuticals has also been the world's leader in the invention of new uses for amylin (and amylin agonists) in the treatment of human disease. It has also led the discovery and development of new formulations and dosages of amylin and compounds that act as agonists of amylin.

The invention that is the subject of this application was made at Amylin Pharmaceuticals, Inc. In addition to this application, Amylin Pharmaceuticals is also the owner of all the patents cited by the Patent Office in support of its rejection of claims. Furthermore, Amylin Pharmaceuticals scientists are the authors of all the publications relied on by the Examiner in formulating his rejections. Thus, all of the information used by the Patent and Trademark Office in considering the rejection of claims in the instant application is based upon inventions made at Amylin Pharmaceuticals, Inc. That said, it is important to understand that over the years since the company was founded in 1987, Amylin Pharmaceuticals has been careful to draw each of its patents and patent applications to separately patentable inventions. This is true with the instant case as well.

The claimed invention is directed to the treatment of obesity in a human subject using amylin or an amylin agonist (e.g., Specification at pages 12-13, and 27-31). Dependent claims 2-6 are directed to important other inventions, namely, to treatment of obesity with "amylin agonist analogues," including ^{25,28,29}Pro-h-amylin (e.g., claims 2-3; specification, pages 13-14), treatment of obesity by "subcutaneous" administration of the claimed compositions (e.g., claim 4; specification, page 28), treatment of obesity using particularly efficacious frequencies of administration (e.g., claim 5; specification, pages 28-29), and treatment of obesity using specific dosages (e.g., claim 6; specification, pages 28-29).

Amylin, a peptide synthesized and isolated from pancreatic cells, has traditionally been used in the treatment of various forms of diabetes, a disorder characterized by the inability to regulate blood sugar levels. In Type I diabetes, amylin has been shown to be deficient and combined replacement with insulin has been proposed as a preferred treatment over insulin alone in all forms of insulin-dependent diabetes. The use of amylin and amylin agonists for the treatment of diabetes mellitus is the subject of Amylin Pharmaceuticals U.S. Patent No. 5,175,145, issued Dec. 29, 1992. Pharmaceutical compositions containing amylin and amylin plus insulin are described in U.S. Patent No. 5,124,314, issued Jun. 23, 1992.

Before the instant invention, however, amylin and agonists thereof had never before been used or suggested to treat obesity in humans. In fact, studies had actually demonstrated the opposite, namely, the effective and preferred use of amylin ***antagonists***, i.e., compounds that actually ***block*** the normal effects of amylin, to treat obesity. *See, e.g.*, Amylin Pharmaceuticals' U.S. Patent No. 5,280,014, issued January 18, 1994, and U.S. Patent No. 5,364,841, issued November 15, 1994, both entitled, "Treatment of obesity and essential hypertension and related disorders." Both patents are directed to the treatment of obesity with amylin antagonists in order to block amylin activity, not agonists to enhance such activity. Claim 2 of the '014 patent, for example, reads:

> "A method for the treatment of obesity in a subject comprising administering to said subject an amount of an ***amylin antagonist*** effective ***to reduce amylin activity*** in said subject".

Claim 2 of the '841 patent reads:

> "A method for the treatment of obesity in a subject comprising administering to said subject an amount of an ***amylin receptor antagonist*** effective ***to reduce amylin activity*** in said subject."

The Examiner does not mention any of this work in his analysis and rejection of the instant claims that are directed to the use

of amylin agonists in the treatment of obesity, an invention that is supported in the application with human clinical data.

Other work from Amylin Pharmaceuticals that is relied on by the Examiner in his rejection of claims relates to appetite suppression. Amylin Pharmaceuticals' U.S. Patent No. 5,739,106, issued to Rink *et al.* on April 14, 1998, for "Appetite Regulating Compositions" on an application filed June 76, 1995. That patent, however, is directed to a combination therapy, namely, the use of amylin in conjunction with cholecystokinin ("CCK") to effect appetite suppression. It further teaches away from the instant invention by reporting that administration of amylin alone has "no measurable effect on food intake" at 1 µg/kg. Thus, the doses of amylin agonist described and claimed in the instant application are taught by the Rink *et al.* patent to have ***no effect*** on appetite suppression, let alone obesity.

Issues

1. Whether claims 1-3, directed to the treatment of obesity in humans using amylin or an amylin agonist, are patentable under 35 U.S.C. § 102(e) over Rink *et al.*, U.S. Patent No. 5,739,106 ("the Rink patent"), which teaches appetite suppression in rats using a CCK/amylin combination composition, and which is

accompanied by unsubstantiated statements of appetite suppression in mammals generally.

2. Whether claims 4-6, which are directed to the treatment of obesity in humans using amylin or an amylin agonist administered subcutaneously, 1-4 times per day, and in 30-300 μg dosages, are patentable under 35 U.S.C. § 103 over the Rink patent in view of Amylin Pharmaceuticals' Gaeta *et al.*, U.S. Patent No. 5,686,411 ("the Gaeta patent"), which teaches specific, new amylin agonists and their use in the treatment of diabetes, but not obesity.

3. Whether claims 1-6, which are directed to the treatment of obesity in humans using amylins and amylin agonists, are patentable under 35 U.S.C. § 103 over the following Amylin Pharmaceuticals' scientific publications and patents: Kolterman *et al.* (I) or Kolterman *et al.* (II) or Moyses *et al.* or Thompson *et al.*, in view of Cooper *et al.* and the Rink patent, where each of Kolterman I, Kolterman II, Moyses, and Thompson only teach the treatment of diabetes, not obesity, where Cooper actually teaches the use of amylin antagonists, and not agonists, and when the Rink patent only teaches appetite

suppression with CCK/amylin combination compositions at different dosages in rodents?

Grouping of Claims

Claims 1-6 **do not** stand or fall together.

Claim 2 is separately patentable for the reason that it is directed to amylin agonist analogues, and as such may have special value, e.g., in efficacy, potency, stability, and/or synthesis. An example is the specific amylin agonist analog, ^{25,28,29}Pro-h-amylin, otherwise known as "pramlintide," which is specifically recited in claim 3 and for which exists intensive clinical data supporting its efficacy. *See, e.g.*, Specification, pages 30-31.

Claim 4 is further directed to subcutaneous administration, which is a preferred mode of delivery over oral ingestion, for which much more drug (5-10X) would need be taken to achieve a similar result. *See* Specification, page 28.

Claim 5 is separately patentable and is directed to the frequency of administration of the obesity treatment. Data provided in the application supports a preferred indication for use over other administration frequencies. *See, e.g.*, Specification, pages 28-29.

Claim 6 is separately patentable and is directed to dosages of 30-300 μg to be administered between 1 and 4 times daily per

claim 5. As set forth in the Specification, these dosages and frequencies of administration are shown especially effective in promoting weight loss.

Argument

1. CLAIMS 1-3 ARE PATENTABLE UNDER 35 U.S.C. §102(E) OVER RINK *ET AL.*, U.S. PATENT NO. 5,739,106 ("THE RINK PATENT"), BECAUSE THE RINK PATENT ONLY DISCLOSES AMYLIN-INDUCED APPETITE SUPPRESSION IN RODENTS, WHEREAS THE INSTANT CLAIMS ARE DIRECTED TO AND ENABLING OF THE TREATMENT OF OBESITY IN HUMANS, AND FURTHER, BECAUSE THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.

The Examiner rejected claims 1-3 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 5,739,106, issued to Rink *et al.* on April 14, 1998 from an application filed June 7, 1995 ("the Rink patent"). Claim 1 of the present application is directed to the use of an amylin or an amylin agonist to treat obesity in a human subject. Claim 2 depends from Claim 1 and specifies that the amylin agonist is an amylin agonist analogue. Claim 3 specifies that the amylin agonist analogue of Claim 2 is the amylin agonist analogue known as "pramlintide" (^{25,28,29}Pro-h-amylin). As noted above, the Rink patent nowhere mentions the use of amylin or amylin agonists for the treatment of obesity, and indicates that administration of amylin alone into experimental animals "has no measurable effect on food intake" at 1 µg/kg.

The Examiner states that this § 102 rejection was maintained on the assertion that:

> the claims, as currently drafted, use the open claim language "comprising" and do not exclude the administration of any other substance other than amylin or amylin agonist. Claims 83-85 [of the Rink patent] do encompass methods for control of body weight or control of appetite or suppression of food intake in a mammal comprising administering an effective amount of an amylin agonist, in particular ^{25,28,29}pro-h-amylin. Amylin agonist is administered in an amount of about 0.1 µg/kg/day (column 95, lines 1-8) and 1-3 times a day (see column 21, lines 26 and 27). The amylin agonist can be s-calcitonin or h-amylin (see column 8, lines 35-38). Further, Rink *et al.* ('106) illustrate that administration of amylin alone did suppress food intake (see Figure 1). Rink *et al.* also discuss the art-recognized fact that amylin reduces food intake significantly in mammals (see paragraph bridging columns 6 and 7)

Office Action, June 24, 1999, page 2.

Section 102 of Title 35 of the United States Code provides, in pertinent part: "A person shall be entitled to a patent unless . . . (e) the invention was described in a patent granted on an application for another filed in the United States before the invention thereof by the applicant for patent . . .." To qualify as anticipatory art under this section of the statute, the patent must disclose each and every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 44 USPQ2d 1429 (Fed. Cir. 1997). A claim is anticipated and thus not novel within the meaning of Section 102 only if it can be proved that a single prior art

reference discloses each element of the claimed invention. Anticipation of a patent claim requires a finding that the claim at issue "reads on" a prior art reference. *See Titanium Metals Corp. v. Banner,* 778 F.2d 775, 781, 227 USPQ 773, 778 (Fed. Cir. 1985). When the claim in issue is directed to a process, as in the instant case, anticipation requires identity of the claimed process and the process of the prior art. Thus, the claimed process, including each step of the process, must be described or embodied in a single reference. *Glaverbel Societe Anonyme v. Northlake Marketing,* 45 F.3d 1550, 1554, 33 USPQ2d 1496, 1498 (Fed. Cir. 1995).

In addition, the disclosure must enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc., v. Guardian Industries Corp.*, 75 F.3d 1558, 37 USPQ2d 1618 (Fed. Cir. 1996); *see also In re Spada,* 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)).

As demonstrated below, it is clear that the Rink patent does not describe the methods of treating obesity disclosed in the present application. The Rink patent fails either to teach or to enable the inventions of the appealed claims. Appealed claim 1, for example, reads:

> A method of treating obesity in a human subject comprising administering to said subject an effective amount of a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist.[1] [Emphasis added.]

Looking to the claim, it is apparent that it is directed to the treatment of obesity in humans using amylin or an amylin agonist.

The Rink patent, by comparison, does not describe the treatment of obesity in humans using amylin or an amylin agonist. The Rink patent is directed to (1) a composition that includes an amylin agonist admixed with a cholecystokinin ("CCK") agonist or (2) a composition that includes a hybrid peptide that incorporates features of amylin agonist peptides and CCK agonist peptides. The basis for the Rink *et al.* invention is not the use of amylin or an amylin agonist as a food intake inhibitor. To the contrary, the Rink patent sets out the basis for the patent in the Summary of the Invention at Column 7 of the Rink patent, where it is reported that even an intraperitoneal injection (let alone a subcutaneous injection) of 1μg/kg of amylin had no effect on food intake. The Rink patent states:

---

[1] The Examiner's quotation presumably reflects a position held prior to entry of the specific claim language "a composition comprising an anti-obesity agent consisting of", which occurred after final rejection.

> Applicants have discovered that amylin agonists and CCK agonists when administered together, have a synergistic effect on reduction of food intake. The present application describes the use of an amylin agonist in conjunction with a CCK agonist for the control of food intake. For example, an IP injection of 1.0 μg/kg CCK-8 or of 1.0 μg/kg rat amylin has no measurable effect on food intake. But administration of 0.1 μg/kg of each peptide causes a substantial reduction of food intake about equivalent to that seen with 100 μg/kg of either peptide alone [the Rink patent, column 7, lines 14-23; emphasis added].

The instant application, on the other hand, describes and claims the use of amylin or amylin agonists alone in the treatment or prevention of obesity in a human subject. The application describes the use, for example, of amylin or amylin agonist doses in the range of 30 μg to 300 μg. *See* pending claim 6, which reads, "A method according to claim 5 wherein said amylin or amylin agonist is administered in an amount from 30 μg/dose to 300 μg/dose."[2] Given that the average adult human weighs about 70 kg, the instant application thus teaches that effective doses of an amylin or an amylin agonist alone for the treatment or prevention obesity in such subjects range from about 0.43 to about 4.3 μg/kg. Conversely, the Rink patent reports that a 1.0 μg/kg dose (equivalent to about 70μg/dose in an adult human) had

---

[2] Claim 5 is directed to the treatment or prevention of obesity by the subcutaneous administration of an amylin or amylin agonist from 1 to 4 times per day.

no effect on food intake. In fact, the Rink patent reports that the preferred synergistic doses of CCK combined with an amylin agonist (0.1 μg/kg of each peptide) were those "equivalent to that seen with 100 μg/kg [a 7000 μg dose in an 70 kg adult human] of either peptide alone." Thus, the Rink patent could only be read to provide that amylin and amylin agonists administered as described and claimed in the instant treatment of obesity application have "no measurable effect" on food intake, let alone obesity. Applicants thus submit that Rink *et al.* does not within the meaning of 35 USC § 102 teach the use of an amylin agonist alone for controlling appetite. Nor does it describe treating obesity in human subjects as set forth in the pending claims within the meaning of 35 USC § 102 and the anticipation rejection cannot stand.[3] Applicants request that the rejection be reconsidered and withdrawn.

---

[3] The Examiner states that claims 83-85 of Rink *et al.* encompass methods for control of body weight in a mammal comprising administering a therapeutically effective amount of an amylin agonist such as $^{25, 28, 29}$pro-h-amylin. As previously pointed out, none of these claims refer to the administration of an amylin agonist alone. Claims 83-85 each refer to the administration of a composition of "any of claims 1-6, 17, 18, 32, 33, 46, 47, 61, 63 or 72," all of which are directed to compositions that comprise an amylin agonist and a CCK agonist admixed together (claims 1-6), to hybrid peptides comprising covalently linked amylin agonist and CCK agonist peptides (claims 17, 18, 32, 33, 46, 47, and 61), or to other specific hybrid peptides (claims 63 and 72).

In sum, the Rink patent is directed to the combination of an amylin admixed with a CCK, and for the express purpose of inhibiting food intake, not treating obesity. Claims 83-85 of the Rink patent are consonant in that they expressly incorporate this combinational effect, which effect is entirely absent in the Applicants' instant claims and teachings. The focus and effect of the two disclosures is thus critically different.

Moreover, and consistent with the above, the Examiner's assertions that the paragraph bridging columns 6 and 7 of the Rink patent reflect an alleged "art-recognized fact" that amylin can inhibit appetite suppression in all mammals is the product of hindsight after having had the benefit of reading the instant application, and not an accurate characterization of the passage. The passage reads:

> Amylin has been reported to reduce food intake in rats and mice when administered into the brain. Balasubramaniam et al., Peptides 12:919-924 (1991); Chance et al., Brain Res. 539:352-354 (1991). An anorectic effect of amylin has been reportedly observed after intraperitoneal (IP) injection in mice and rats. Morley and Flood, Peptides 12:865-869 (1991); Morley et al., Pharmacol. Biochem. Behav. 44:577-580

The Examiner's reliance on the scope of claims 83-85 from the Rink patent also violates the Federal Circuit's pronouncement in *In re Benno*, 768 F.2d 1340, 1346, 226 USPQ 683, 686 (Fed. Cir. 1985), that in assessing the alleged prior art effect of a patent, what may fall within the breadth of that patents claims is not an appropriate measure of the work of that patent as alleged prior art.

> (1993). It has also been reported that amylin, when administered IP in rats at a dosage of 0.5 mu.g/kg, significantly decreased food intake. Lutz et al., Physiology & Behavior 55:891-895 (1994). Reported dose-dependent side effects of injected amylin agonist in man include nausea, vomiting, diarrhea, flushing and postural hypotension. See, e.g., Moyses and Kolterman, supra.

(emphasis added).

Thus, the passage mentions that appetite suppression "has been reported" in rats and mice, but there is absolutely no mention there of a similar effect in other mammals, and certainly not humans. In fact, the paragraph concludes with several amylin effects in humans, none of which recite appetite suppression, let alone effects on obesity. The Examiner's reliance on this particular passage of the Rink patent is thus misplaced.

When it is understood that the appealed claims are directed to the treatment of obesity in humans whereas the Rink patent, at best, teaches the combined effects of amylin and CCK as measured by appetite suppression in rodents, Rink fails to anticipate claims 1-3. Reversal of this ground of rejection is therefore both appropriate and requested.

2. CLAIMS 4-6 ARE PATENTABLE UNDER 35 U.S.C. § 103(A) OVER THE RINK PATENT IN VIEW OF GAETA *ET AL.*, US PATENT NO. 5,686,411 (THE GAETA PATENT), BECAUSE THE INSTANT CLAIMS ARE DIRECTED TO PARAMETERS USEFUL IN TREATING OBESITY WHEREAS THE '411 PATENT CITED BY THE EXAMINER PROVIDES IRRELEVANT PARAMETERS DIRECTED TO THE TREATMENT OF AN ENTIRELY DIFFERENT AFFLICTION, DIABETES.

The claims which form the basis for the instant ground of rejection, 4-6, build on independent claim 1 above, and further incorporate the additional claim features of subcutaneous administration (claim 4), administration 1 to 4 times per day (claim 5), and dosage amounts of 30-300 μg (claim 6). These claims stand rejected under 35 USC § 103(a) as allegedly obvious over the Rink patent in view of Gaeta *et al.*, U.S. Patent No. 5,686,411 (the Gaeta patent).

In maintaining the rejection, the Examiner has inappropriately combined the teachings of the Rink patent with the teachings of the Gaeta patent. The Examiner's reasons for the rejection are as follows:

> The references of Rink et al and Gaeta et al have been applied in this rejection because they qualify as prior art under subsection (e) of 35 U.S.C. §102 and accordingly are not disqualified under USC §103(a).[4]
>
> The teachings of Rink et al. have been explained above. Rink et al. do not teach the specific doses, times and route of administration recited in claims 4-6.
>
> Gaeta et al. teach that "[a]s will be recognized by those in the field, an effective amount of of therapeutic agent will vary with many factors including the age and weight of the patient, the

---

[4] It should be noted that, effective May 29, 2000 for applications filed after November 29, 2000, the Examiner's statement no longer holds true. New statutory changes to 35 USC §103(c) have been implemented under the American Inventors Protection Act of 1999 that have the effect of disqualifying commonly owned or obligated art as of the date of invention.

patient's physical condition... and other factors". Typical doses contain 0.1 to 1.0 mg of an amylin agonist compound and this range covers the one recited in claim 6. The composition may conveniently be provided in the form suitable for subcutaneous administration (column 7, lines 37-40). It is further taught that a "suitable administration format may best be determined by a medical practitioner for each patient individually" (column 7, lines 45-47), and that suitable "doses are readily determined by those in the art" (column 8, lines 62 and 63).

Further, the specific time period of administration is generally dose dependent and the time is determined based on standard treatment regimens. Generally, the dosage and periods of administration would vary with the age, sex, clinical condition, extent of the disease in the patient and can be further determined by one skilled in the art. The dosage and time period can also be determined or adjusted by a physician on an individual basis. The different times and route administration can be determined by routine experimentation and thus would have been obvious to one of skill in the art.

It would have been obvious to one or ordinary skill in the art at the time the invention was made to use Rink's method of controlling body weight, reducing food intake and suppressing appetite in mammals including humans by administering an amylin agonist at does, time periods and the route recited in the instant claims since these can be readily determined based on the weight, age and physical condition of the patient as taught by Gaeta et al. or by routine experimentation.

Office Action, Paper 6, pp. 4 bridging 5, ¶9.

It is well understood that before the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992) (citing *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988)). There must be some objective suggestion in the art to do what Applicants have claimed. *See, e.g., Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (Bd. Patent App & Inf. 1992), which confirms that:

> In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988). Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

Further, the teaching or suggestion to combine must be "clear and particular," and not merely "[b]road conclusory statements regarding the teaching of multiple references." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Also, an alleged reference "must be read not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). Moreover, references may not be combined if they are not analogous art. *In re Clay*, 966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992). The test for

whether art is analogous art is whether the art is from the "same field of endeavor" and, if not, whether the reference is "reasonably pertinent" to the particular problem with which inventor is involved. *Id.; In re GPAC Inc.*, 57 F.3d 1573, 35 USPQ2d 1116 (Fed. Cir. 1995).

Further, in making the obviousness determination, one must not import the solution into the problem. To do so admits of impermissible hindsight. *Monarch Knitting Machinery Corp. v. Fukuhara Industrial & Trading Co., Ltd.*, 139 F.3d 1009, 45 USQP2d 1977 (Fed. Cir. 1998). Put differently,

> to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

In re Fine, 837 F.2d at 1074, 5 USPQ2d at 1598 (Fed. Cir. 1988), citing *W.L. Gore Assoc. v. Garlock*, 721 F.2d 1540, 1553 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Applying the law to the instant rejection, the claims relate to the treatment of obesity in humans whereas the Gaeta patent, by contrast, is directed to diabetes treatment. The Gaeta patent is therefore not relevant, analogous art. Even assuming *arguendo* that it is, there is no proper motivation to

combine it with the Rink patent to provide a *prima facie* case of obviousness.

Obesity and diabetes are two entirely different afflictions that have only an occasional coincidence. It is therefore incorrect for purposes of legal obviousness to relate the obesity and diabetes treatment arts to one another simply because some diabetics also happen to be obese, and vice-versa. As is clear even to the lay person, many diabetics are not obese and many obese persons are not diabetics. Thus, there is simply no proper motivation or suggestion to combine the diabetes treatment parameters taught by Gaeta with the appetite suppression teachings of Rink, especially when Rink teaches appetite suppression in rodents and not obesity treatment in humans. More fundamentally, the Gaeta patent does not supply what the Rink patent lacks. The Gaeta patent only speaks to diabetes treatment, and the Examiner's reliance on Gaeta for treatment particulars for obesity is thus misplaced. Thus, even combining the Rink and Gaeta teachings does not result in the instantly claimed invention, and conclusory statements by the Examiner cannot fill the gap. *In re Dembiczak, supra.*

This position is even more pronounced (and the Examiner's position hence even more strained) when one considers the specifics of dependent claims 4-6. Claim 4, for example, is directed to subcutaneous administration. Although this mode of

administration may be useful for diabetes treatment, it says nothing of obesity treatment. Similarly, claim five is directed to drug administration 1 to 4 times daily. Nowhere is this particular claim parameter found in either of the Rink or Gaeta patents nor can the dose administration ideas of those patents, whatever relevance they may have for diabetes, be said to apply to obesity. Lastly, claim 6 builds from claim 5 and further specifies administration amounts of 30-300 μg. Nowhere in Rink, Gaeta, or their combined teachings is this particular claim limitation for weight loss even remotely suggested.

Further supporting this, and believed sufficient alone to rebut the Examiner's position, the reference Cooper *et al.* was cited by the Examiner as a basis for rejection 3. However, and as explained further below, Cooper actually "teaches away" from the desirability of combining the Rink patent with the Gaeta patent, or, for that matter, the Rink patent with any other disclosure that speaks to amylin agonist use in the treatment of diabetes.

Additionally, and as already discussed, the Rink patent shows how amounts of amylin specified as useful in the instant invention have absolutely no effect on appetite suppression in rodents. Further, the Rink patent only teaches amylin use in conjunction with CCK. If obesity treatment using amylin alone was so obvious, why did Rink not discuss or claim it? The

answer is that with the data available at the time, no real prediction could be made. In fact, as Cooper *et al.* note, predictions to the contrary were made.

These contrary teachings have already been made of record and, incomprehensibly, have not been appreciated for their value so clear under the law. In maintaining the rejections, the Examiner contravenes law that provides that evidence of "teaching away" must be considered, and that such can completely undermine the necessary motivation to combine references. In *Gambro Lundia AB v. Baxter Healthcare Corp.* 42 USPQ2d 1378, 1383 (Fed. Cir. 1997), for example, the Federal Circuit reversed a district court decision holding various claims of a patent invalid for obviousness because strong evidence existed that the art actually taught away from the claimed combinations. In the present case, the line of development flowing from the disclosure of the alleged reference is unlikely to be productive of the result sought by the applicant and is actually antithetical to the claims because amylin agonists as taught by the claims would be expected in the art to have the exact opposite effect of antagonists.

Similarly, in *Monarch Knitting Machinery Corp. v. Sulzer Moat GmbH*, 45 USPQ2d 1977 (Fed. Cir. 1998), the Court upheld a denial of summary judgment where strong evidence of teaching away existed in the same art. In the instant case, this

position is fortified because the art is not the same art. Diabetes treatment is not at all like obesity treatment. Further, when the Cooper reference is considered, a person of ordinary skill is discouraged from following the path of agonists as claimed, and instead pursues antagonists. The person of skill would, reading the cited Cooper article, be more than skeptical – they would be dissuaded altogether. This is important because, even as acknowledged by the Federal Circuit, even general skepticism that does not amount to an actual teaching away is still "relevant and persuasive evidence" of nonobviousness. See *Gillette Co. v. S.C. Johnson & Son, Inc.* , 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). The facts here transcend this statement to a truism that is undeniable for the instant case.

PPG Industries Inc. v. Guardian Industries Corp., 37 USPQ2d 1618 (Fed. Cir. 1997) is in agreement. In *PPG Industries*, a preliminary injunction based on alleged infringement of a patent was upheld over allegations that the patent claims were obvious. The Court noted that credible and substantial evidence of unobviousness existed because teachings in the art taught away from the claimed invention.

In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993), further fortifies the Applicants' position. There, the Federal Circuit reversed a Board rejection because of a prior art reference that

taught away from the claimed invention. The Court held that this evidence could not "fairly suggest" the combination of art references necessary to sustain the rejection.

Finally, the Board of Patent Appeals and Interferences, in *Ex parte The Goodyear Tire and Rubber Co*, 230 USPQ 357 (BPAI 1985), reversed rejections founded on alleged obviousness, emphasizing the significance of art references in the prosecution record that taught away from the claimed invention. Although *Goodyear* concerned technology different from the technology at bar, significantly, in *Goodyear* as here, evidence was proffered by the Applicant during prosecution that was either not considered or else misunderstood by the examiner. This evidence was found dispositive by the Board.

Accordingly, it is submitted that the present rejection cannot stand and should be reversed.

3. CLAIMS 1-6 ARE PATENTABLE UNDER 35 U.S.C. § 103(A) OVER KOLTERMAN *ET AL.* (I) OR KOLTERMAN *ET AL.* (II) OR MOYSES *ET AL.* OR THOMPSON *ET AL.* IN VIEW OF COOPER *ET AL.* AND THE RINK PATENT BECAUSE NONE OF THE CITED DOCUMENTS ARE DIRECTED TO THE TREATMENT OF OBESITY, AND FURTHER BECAUSE THE EXAMINER HAS IGNORED EVIDENCE THAT ACTUALLY TEACHES AWAY FROM WHAT THE APPLICANTS CLAIM.

The Examiner has rejected claims 1-6 under 35 USC § 103(a) as allegedly obvious over Kolterman *et al.* (*Diabetologia*, 39: 492-499, April, 1996) (I) or Kolterman *et al.* (WO/96/40220) (II) or Moyses *et al.* (Diabet. Med. 13 (suppl. 1): 34-38, September,

1996) or Thompson *et al.* (Diabetes 46: 632-636, April 1997) in view of Cooper *et al.* (Biochim. Biophys. Acta 1014(3): 247-258, 1989, abstract) and the Rink patent. September 16, 1998 Office Action, Paper 6, page 5, ¶ 10. In making the rejection, the Examiner alleged:

> Kolterman *et al.* (I) teach a method of treatment of patients with diabetes mellitus by subcutaneous administration of 30, 100, or 300 ug of pramlintide or AC137 (i.e. $^{25,\ 28,\ 29}$pro-h-amylin) three times a day (abstact and page 493).
>
> Kolterman *et al.* (II) teach methods of treating type II diabetes mellitus comprising administering a therapeutically effective amount of an amylin agonist such as $^{25,\ 28,\ 29}$pro-h-amylin, s-calcitonin an h-amylin (abstract and claims). $^{25,\ 28,\ 29}$pro-h-amylin has been found to possess more desirable solubility and stability characteristics compared to human amylin (page 13). It is taught that a suitable administration format may best be determined by a medical practitioner for each patient individually (page 19). "The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range as well as upon the age, weight and condition of the individual". Administration may be preferably by subcutaneous injection. Amylin agonists such as $^{25,\ 28,\ 29}$pro-h-amylin may be administered in a single or multiple does, for example, two (BID), three (TID), and/or four (QID) times per day. BID doses range from about 30 ug to 150 ug BID, more preferably from about 50 ug to 60 ug BID. TID doses range from about 30 ug to 60 ug QID, more preferably about 30 ug QID. These doses have been demonstrated to be effective in various human clinical trials and are administered subcutaneously (page 21).
>
> Moyses *et al.* teach a method of treatment of human diabetetic patients comprising administering pramlintide ($^{25,\ 28,\ 29}$pro-h-amylin) by subcutaneous injections in doses of 30 ug, 100 ug or 300 ug t.i.d. (pages 36 and 38).

Thompson *et al.* teach a method of treating human subjects with diabetes, a clinical condition often associated with obesity, by administering subcutaneously 10, 30, or 100 micrograms (which falls in the dose range recited in claim 6) q.i.d. of Pramlintide, an amylin agonist analogue which "incorporates proline substitutions at positions 25, 28, and 29 of the amylin molecule" (see page 632).

Kolterman *et al.* or Kolterman et al or Moyses et al do not teach a method of treating or preventing obesity by administering pramlintide to a human subject.

Rink *et al.* teach the therapeutic effectiveness of $^{25,\ 28,\ 29}$pro-h-amylin, an amylin agonist, in controlling body weight, reducing food intake and suppressing appetite in mammals including humans (abstract and column 11, lines 25 and 26).

Cooper *et al.* teach that "obesity which frequently accompanies" type 2 or non-insulin dependent diabetes mellitus (NIDDM) is a result of, rather than a risk factor for, NIDDM (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's method (I and II) or Moyses' or Thompson's method of treating type 2 diabetes, which is frequently associated with overweight, with $^{25,\ 28,\ 29}$pro-h-amylin to treat obesity because, Rink *et al.* teach that $^{25,\ 28,\ 29}$pro-h-amylin is also effective in controlling body weight, reducing food intake and suppressing appetite in humans, and that there is an art-recognized clinical need for weight reduction in patients suffering from type II diabetes mellitus. Since Cooper et al teach that obesity is a result of NIDDM or type II diabetes, one of ordinary skill in the art would be motivated to produce the instant invention for the expected benefit of preventing NIDDM from advancing to or resulting in obesity. One of ordinary skill in the art would have had a reasonable expectation of success in using Kolterman's (I and II) or Moyses' or Thompson's method of treating type II diabetes also for treatment of obesity because these two associated clinical conditions share the

common pathogenetic mechanisms as taught by Rink *et al.*

Id. (italics in the original; underscore added).

Applicants herein incorporate by reference arguments 1 and 2 above respecting the teachings of Rink and the law governing obviousness. In addition, and of fundamental import in traversing the instant rejection, it is the law that objective evidence of nonobviousness must be considered when presented. *In re Mayne*, 104 F.3d 1339, 41 USPQ2d 1451 (Fed. Cir. 1997); *In re Huang*, 100 F.3d 135, USPQ2d 1685 (Fed. Cir. 1996) (citing *In re Serkaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983)); *In re GPAC, Inc.*, 57 F.3d 1573, 35 USPQ2d 1116 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988)("Evidence that supports, rather than negates, patentability must be fairly considered"); *In re Chupp*, 2 U.S.P.Q.2d 1437 (Fed. Cir. 1987). References are to be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). In general, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Gurley*, 27 F.3d 551, 553,

31 USPQ2d 1130, 1131 (Fed. Cir. 1994), citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966) These tenets of the patent law serve "as insurance against the insidious attraction of the siren hindsight." W.L. *Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d at 1553, 220 USPQ at 313.

At least two flaws exist in the Examiner's formulation and maintenance of the instant rejection. First, none of the cited documents is directed to obesity treatment; most are directed to the treatment of diabetes, the only one that is not, Rink, is directed to appetite suppression in rodents using combinational formulations, and not amylin alone. Second, the only documents that the Examiner purports to relate diabetes and obesity are Thompson and Cooper. However, Applicants fail to note any such relation in Thompson, and a closer look at Cooper reveals that it teaches exactly the opposite of what the Examiner alleges it to teach:

> Several lines of evidence now implicate elevated amylin levels in the pathogenic mechanisms underlying NIDDM, and suggest to us that the obesity which frequently accompanies this syndrome is a result of rather than a risk factor for, NIDDM.

Cooper *et al.*, *Biochim Biophys. Acta* 1014(3): 247-258, 1989, abstract.

Thus, a reasonable interpretation of Coolper is that elevated amylin levels actually increase diabetes and obesity

incidence, not decrease them. This is the exact opposite of what the Applicants claim, and is confirmed by other evidence presented by the Applicants during prosecution - evidence that apparently was misconstrued and/or not considered by the Examiner for its true merit.

In this regard, Applicants refer the Board to Applicants' responses of March 16, 1999 and December 23, 1999. In those responses, Applicants submitted U.S. Patent Nos. 5,364,841 and 5,280,014 issued to Cooper (the same Cooper cited by the Examiner) to show that obesity was treated in the art using amylin ***blockers*** or ***antagonists***, and that the art viewed the proposed use of amylin agonists with skepticism due to the fact that such use would be expected to have an opposite effect to that desired, i.e., the patient would actually be expected to gain and not lose weight.

That the Examiner only cited and relies on amylin agonist patents relating to the treatment of diabetes and did not cite treatment of obesity patents teaching amylin antagonist use and preference contravenes the law that a reference "must be read not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986); *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). As

demonstrated, the "whole" of the art was not considered by the Examiner.

That the Examiner misconstrued or ignored the proffered evidence is further reflected in his subsequent lodging of a rejection over the '014 and '841 patents, introduced by the Applicants to rebut the first rejection:

> Cooper et al ('014) teach a method of treating obesity in a subject comprising administering an effective amount of CGRP 8-37, which is an amylin agonist. . . .
>
> Cooper et al ('841) teach a method of treating obesity in a subject comprising administering an effective amount of CGRP 8-37, which is an amylin agonist.

Office Action, Paper 13, pg.6, ¶ 12 (emphasis added).

This is incorrect for the reason that these references teach antagonists and not agonists. Upon the Applicants' correction of the Examiner on this point, the Examiner withdrew the rejection. See Advisory Action, January 21, 2000, Paper 18. However, the Examiner did not re-evaluate the propriety of the existing rejections in light of this error.

Thus, the Cooper reference on which the Examiner maintains the instant rejection actually teaches away from the Applicants' claimed invention, and cannot as a matter of law be said to motivate one of ordinary skill in the art to combine the references as the Examiner has done. One of skill would actually predict failure based on this reference, be

discouraged, and as a consequence pursue a different avenue altogether.

As for the Examiner's argument that because "weight reduction is often the recommended first course of action for patients suffering from type II diabetes mellitus as taught by Rink *et al.*, one of ordinary skill in the art would be motivated to produce the instant invention for the expected benefit of preventing NIDDM from advancing to or resulting in obesity," this is circular and could only have been constructed in hindsight based upon the disclosures of the instant application. Applicants are not aware of any statement in the documents relied on by the Examiner that suggest the inventions described and claimed in the instant application.

Indeed, Applicants submit that upon consideration of the lack of teaching in the cited documents, and upon consideration of the antagonist and anorexia patents cited by Applicants that actually teach away from their inventions, coupled with a fuller understanding of what the Rink and Cooper references actually teach, one is inescapably lead to a conclusion of nonobviousness.

Accordingly, reversal of the Examiner's rejection is sought.

CONCLUSION

For all of the foregoing reasons, Applicants submit that all outstanding rejections of claims and objections to the specification should be reversed and seek an early ruling to that effect.

Dated: 7/24/00

Respectfully submitted,

By: _____
Charles S. Berkman
Registration No. 38,077

First Interstate World Center
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
(858) 552-8400

Appendix One

Set forth below is the text of the claims (1-6) involved in this appeal:

1. A method of treating obesity in a human subject comprising administering to said subject an effective amount of a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist.

2. A method according to claim 1 wherein said amylin agonist is an amylin agonist analogue.

3. A method according to claim 2 wherein said amylin agonist analogue is ^{25,28,29}Pro-h-amylin.

4. A method according to claim 1 wherein said amylin or amylin agonist is administered subcutaneously.

5. A method according to claim 4 wherein said amylin or amylin agonist is administered from 1 to 4 times per day.

6. A method according to claim 5 wherein said amylin or amylin agonist is administered in an amount from 30 μg/dose to 300 μg/dose.